Vincenzo Cirulli

Cadherins in Islet β-Cells: More Than Meets the Eye

Diabetes 2015;64:709–711 | DOI: 10.2337/db14-1662

In 1975, Orci et al. (1) reported that human islet cells contain specialized membrane domains that are compatible with the ultrastructural features of two types of intercellular junctions: tight junctions and gap junctions. Since then, numerous reports have demonstrated critical functions for these cell–cell junctional complexes in islet cells (2–8). Eventually, a number of proteins were identified that regulated cell aggregation, islet cell–type segregation, architectural organization within islets of Langerhans, and state of differentiation, cell growth, and hormone secretion (9–16). Hints that direct islet cell-to-islet cell interactions are required for proper insulin secretion were uncovered in the 1980s when it was observed that single (isolated) β-cells are unresponsive to glucose unless they are given the opportunity to reaggregate into small clusters (17). Even more interesting, it was observed that islet cell types harbor specific cell-to-cell recognition signatures that drive their reaggregation into organoids that have architectural organization indistinguishable from that of native islets (18). These earlier observations have inspired numerous investigations that have led to a more complete understanding of mechanisms regulating islet cell development, architectural organization, and function. In a time of considerable interest in the development of cell-based replacement therapies for diabetes, lessons learned over the past three decades on the function of cell adhesion molecules in islet cells harbor significant translational implications. Hence, promoting the function of select members of the cadherin and integrin families of adhesion receptors plays an important role in the derivation of β-cells from multipotent stem cells; in the isolation, culture, and survival of organ donor–derived islets; and in the successful engraftment and function following transplantation.

This article focuses on adhesion receptors of the cadherin superfamily (19,20), which were referred to as uvomorulin in early work by Kemler et al. (21). Over the past three decades, the function of cadherins in epithelia has evolved from simple cell–cell adhesion molecules that populate subcellular domains called "adherens junctions" to biochemical transducers of signaling processes that contribute to the development, homeostasis, and function of multiple tissues (22–24). Interestingly, cadherins can also function as mechanosensors that affect cell phenotype and function in a dose-dependent manner (25,26). It appears that the transmission of forces from cellular domains occupied by E-cadherin to F-actin filaments is regulated by the intracellular recruitment and accumulation of a number of effector proteins at sites of cell–cell adhesion (27,28). As a result, cells that are in contact with each other through cadherin-mediated junctions sense tension forces that are directly proportional to the degree of actin-anchored cadherin adhesions. In turn, these forces elicit mechanosensory signals from cadherin complexes that ultimately impact on cell phenotype and function in multiple cell types (29,30), including pancreatic islets (31).

In this issue of *Diabetes,* Parnaud et al. (32) uncover direct involvement of E- and N-cadherin in the control of β-cell secretory function in response to glucose. The authors used an elegant approach in which recombinant E-, N-, or P-cadherin ectodomains fused to the Fc of immunoglobulin (E-cad/Fc, N-cad/Fc, or P-cad/Fc) were used for protein mimicry to support islet cell attachment (Fig. 1). This approach allowed them to emulate cadherin-mediated adhesions in single β-cells adherent to a substrate that presented high concentrations of recombinant E-cad/Fc, N-cad/Fc, or P-cad/Fc as if presented by another cell (Fig. 1). Insulin secretion was monitored using a powerful hemolytic plaque assay developed by Salomon and Meda in 1986 that allows probing of the secretion of single β-cells (33–35). This reductionist experimental environment showed a surprisingly close to normal insulin secretory behavior even in single-adherent β-cells.

Essential findings of the new report include the demonstration that cadherin-mediated adhesion in single β-cells, but not α-cells, is positively regulated by glucose and that it is associated with increased insulin secretion.

Diabetes and Obesity Center of Excellence, Department of Medicine, and Institute for Stem Cell and Regenerative Medicine, Department of Pharmacology, University of Washington, Seattle, WA

Corresponding author: Vincenzo Cirulli, vcirulli@u.washington.edu.

See accompanying article, p. 887.

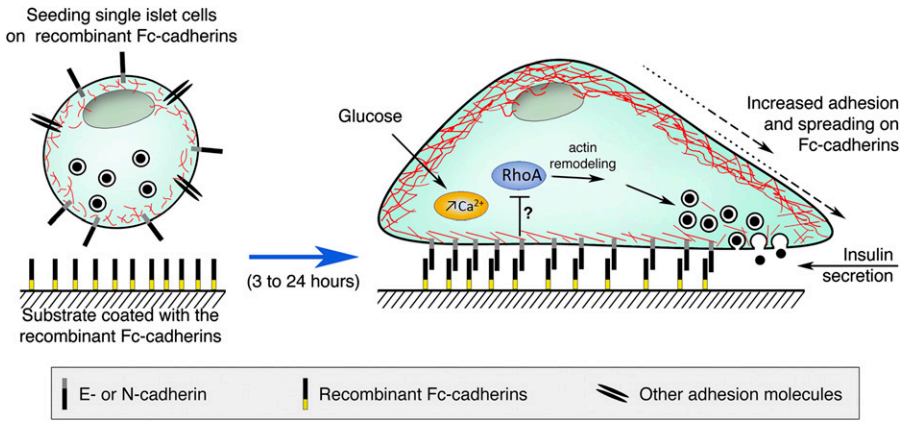

Figure 1—Islet β-cell adhesion to recombinant Fc-cadherins emulates cell–cell interactions and positively regulates glucose-dependent insulin secretion. Seeding of single islet cells on substrates precoated with either E-cad/Fc, N-cad/Fc, or P-cad/Fc (*left*) leads to cell attachment and spreading over a culture period of 3–24 h (*right*). Glucose stimulation results in an increased islet cell spreading and insulin secretion. Blockade of Rho-associated kinase further enhances β-cell attachment and spreading onto E-cad/Fc and N-cad/Fc, a phenotype that positively correlates with enhanced glucose-induced insulin secretion.

As glucose did not affect cadherin gene expression per se, a likely mechanism responsible for this glucose-dependent increase in β-cell adhesion and insulin secretion is the redistribution or reorganization of cortical actin. This has been previously shown to be crucial for proper insulin secretion (36–40). Although the authors let islet cells adhere to recombinant Fc-cadherins for up to 24 h in some experiments, the possible participation of integrin-mediated adhesion to the islet cell–deposited matrix during this short-term culture period, even if present (41,42), may have been minimal as function-blocking antibody treatment to cadherins obliterated the observed effects on adhesion and insulin secretion. This will need to be investigated further because it is possible that cooperation between cadherins and integrins may play a role in the regulation of islet cell polarity and function (43,44).

Collectively, the observation by Parnaud et al. that glucose-induced insulin secretion in individual β-cells can be directly linked to specific cadherin–cadherin ligation offers a new perspective on mechanisms regulating the complex secretory machinery of these endocrine cells. Surely, coupling of insulin secretion with cadherin-mediated cell adhesion is not coincidental or stochastic. Rather, it is likely that these two important processes have coevolved in β-cells to share common signaling mechanisms, one of them being calcium mobilization. Hence, calcium is not only required to elicit glucose-induced insulin secretion but also crucial for the stabilization of cadherin Ca^{2+}-binding ectodomains. Thus, functionally, it activates cell-to-cell adhesion. Finally, in line with the notion that inhibition of Rho-associated kinase, a major effector of RhoA, increases cadherin-mediated adhesion complexes (45), the authors noted that inhibitors of Rho-associated kinase caused a significant increase in β-cell adhesion to recombinant E-cad/Fc (Fig. 1). This observation further adds to a model in which the coordinated regulation and stabilization of cadherin-mediated adhesion complexes, in concert with complementary extracellular signaling cues (46,47), are likely to occur in synergy during glucose-induced insulin secretion. Although the molecular mechanisms that drive glucose-induced enhancement of cadherin ligation and stabilization of adhesions remain to be further elucidated, the new study by Parnaud et al. (32) offers unique opportunities to further delve into the biology of cell-adhesion molecules as regulators of β-cell physiology. Results from this study also open exciting new prospects for the molecular engineering of biocompatible scaffolds that would support islet cell survival and function in islet transplantation settings. Hence, it is only a matter of time before we learn more from the β-cell and its microenvironment.

Acknowledgments. This article is dedicated to the memory of Dominique Guido Rouiller, who first demonstrated the expression and functional requirement of E-cadherin (also known as uvomorulin) in pancreatic islet cell aggregation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Orci L, Malaisse-Lagae F, Amherdt M, et al. Cell contacts in human islets of Langerhans. J Clin Endocrinol Metab 1975;41:841–844
2. Bavamian S, Klee P, Britan A, et al. Islet-cell-to-cell communication as basis for normal insulin secretion. Diabetes Obes Metab 2007;9(Suppl. 2):118–132
3. Benninger RK, Head WS, Zhang M, Satin LS, Piston DW. Gap junctions and other mechanisms of cell–cell communication regulate basal insulin secretion in the pancreatic islet. J Physiol 2011;589:5453–5466
4. Calabrese A, Caton D, Meda P. Differentiating the effects of Cx36 and E-cadherin for proper insulin secretion of MIN6 cells. Exp Cell Res 2004;294:379–391
5. Meda P. Protein-mediated interactions of pancreatic islet cells. Scientifica (Cairo) 2013;2013:621249
6. Meda P, Halban P, Perrelet A, Renold AE, Orci L. Gap junction development is correlated with insulin content in the pancreatic B cell. Science 1980;209:1026–1028
7. Semino MC, de Gagliardino EE, Gagliardino JJ. Islet cells-tight junctions: changes in its number induced by glucose. Acta Physiol Pharmacol Latinoam 1987;37:533–539

8. Serre-Beinier V, Mas C, Calabrese A, et al. Connexins and secretion. Biol Cell 2002;94:477–492
9. Bosco D, Rouiller DG, Halban PA. Differential expression of E-cadherin at the surface of rat beta-cells as a marker of functional heterogeneity. J Endocrinol 2007;194:21–29
10. Cirulli V, Baetens D, Rutishauser U, Halban PA, Orci L, Rouiller DG. Expression of neural cell adhesion molecule (N-CAM) in rat islets and its role in islet cell type segregation. J Cell Sci 1994;107:1429–1436
11. Dahl U, Sjødin A, Semb H. Cadherins regulate aggregation of pancreatic beta-cells in vivo. Development 1996;122:2895–2902
12. Jaques F, Jousset H, Tomas A, et al. Dual effect of cell–cell contact disruption on cytosolic calcium and insulin secretion. Endocrinology 2008;149:2494–2505
13. Møller CJ, Christgau S, Williamson MR, et al. Differential expression of neural cell adhesion molecule and cadherins in pancreatic islets, glucagonomas, and insulinomas. Mol Endocrinol 1992;6:1332–1342
14. Rouiller DG, Cirulli V, Halban PA. Differences in aggregation properties and levels of the neural cell adhesion molecule (NCAM) between islet cell types. Exp Cell Res 1990;191:305–312
15. Rouiller DG, Cirulli V, Halban PA. Uvomorulin mediates calcium-dependent aggregation of islet cells, whereas calcium-independent cell adhesion molecules distinguish between islet cell types. Dev Biol 1991;148:233–242
16. Wakae-Takada N, Xuan S, Watanabe K, Meda P, Leibel RL. Molecular basis for the regulation of islet beta cell mass in mice: the role of E-cadherin. Diabetologia 2013;56:856–866
17. Maes E, Pipeleers D. Effects of glucose and 3′,5′-cyclic adenosine monophosphate upon reaggregation of single pancreatic B-cells. Endocrinology 1984;114:2205–2209
18. Halban PA, Powers SL, George KL, Bonner-Weir S. Spontaneous reassociation of dispersed adult rat pancreatic islet cells into aggregates with three-dimensional architecture typical of native islets. Diabetes 1987;36:783–790
19. Kemler R, Ozawa M, Ringwald M. Calcium-dependent cell adhesion molecules. Curr Opin Cell Biol 1989;1:892–897
20. Takeichi M, Hatta K, Nose A, Nagafuchi A. Identification of a gene family of cadherin cell adhesion molecules. Cell Differ Dev 1988;25(Suppl.):91–94
21. Kemler R, Babinet C, Eisen H, Jacob F. Surface antigen in early differentiation. Proc Natl Acad Sci USA 1977;74:4449–4452
22. Halbleib JM, Nelson WJ. Cadherins in development: cell adhesion, sorting, and tissue morphogenesis. Genes Dev 2006;20:3199–3214
23. Takeichi M. Dynamic contacts: rearranging adherens junctions to drive epithelial remodelling. Nat Rev Mol Cell Biol 2014;15:397–410
24. Vleminckx K, Kemler R. Cadherins and tissue formation: integrating adhesion and signaling. Bioessays 1999;21:211–220
25. de Rooij J. Cadherin adhesion controlled by cortical actin dynamics. Nat Cell Biol 2014;16:508–510
26. Leckband DE, le Duc Q, Wang N, de Rooij J. Mechanotransduction at cadherin-mediated adhesions. Curr Opin Cell Biol 2011;23:523–530
27. Adams CL, Nelson WJ. Cytomechanics of cadherin-mediated cell–cell adhesion. Curr Opin Cell Biol 1998;10:572–577
28. Kemler R. From cadherins to catenins: cytoplasmic protein interactions and regulation of cell adhesion. Trends Genet 1993;9:317–321
29. Huveneers S, Oldenburg J, Spanjaard E, et al. Vinculin associates with endothelial VE-cadherin junctions to control force-dependent remodeling. J Cell Biol 2012;196:641–652
30. le Duc Q, Shi Q, Blonk I, et al. Vinculin potentiates E-cadherin mechanosensing and is recruited to actin-anchored sites within adherens junctions in a myosin II-dependent manner. J Cell Biol 2010;189:1107–1115
31. Jain R, Lammert E. Cell–cell interactions in the endocrine pancreas. Diabetes Obes Metab 2009;11(Suppl. 4):159–167
32. Parnaud G, Lavallard V, Bedat B, et al. Cadherin engagement improves insulin secretion of single human β-cells. Diabetes 2015;64:887–896
33. Bosco D, Orci L, Meda P. Homologous but not heterologous contact increases the insulin secretion of individual pancreatic B-cells. Exp Cell Res 1989;184:72–80
34. Giordano E, Bosco D, Cirulli V, Meda P. Repeated glucose stimulation reveals distinct and lasting secretion patterns of individual rat pancreatic B cells. J Clin Invest 1991;87:2178–2185
35. Salomon D, Meda P. Heterogeneity and contact-dependent regulation of hormone secretion by individual B cells. Exp Cell Res 1986;162:507–520
36. Mizuno K, Ramalho JS, Izumi T. Exophilin8 transiently clusters insulin granules at the actin-rich cell cortex prior to exocytosis. Mol Biol Cell 2011;22:1716–1726
37. Nevins AK, Thurmond DC. Glucose regulates the cortical actin network through modulation of Cdc42 cycling to stimulate insulin secretion. Am J Physiol Cell Physiol 2003;285:C698–C710
38. Pigeau GM, Kolic J, Ball BJ, et al. Insulin granule recruitment and exocytosis is dependent on p110gamma in insulinoma and human beta-cells. Diabetes 2009;58:2084–2092
39. Thurmond DC, Gonelle-Gispert C, Furukawa M, Halban PA, Pessin JE. Glucose-stimulated insulin secretion is coupled to the interaction of actin with the t-SNARE (target membrane soluble N-ethylmaleimide-sensitive factor attachment protein receptor protein) complex. Mol Endocrinol 2003;17:732–742
40. Tomas A, Yermen B, Min L, Pessin JE, Halban PA. Regulation of pancreatic beta-cell insulin secretion by actin cytoskeleton remodelling: role of gelsolin and cooperation with the MAPK signalling pathway. J Cell Sci 2006;119:2156–2167
41. Kaido T, Yebra M, Cirulli V, Montgomery AM. Regulation of human beta-cell adhesion, motility, and insulin secretion by collagen IV and its receptor alpha1beta1. J Biol Chem 2004;279:53762–53769
42. Kaido T, Yebra M, Cirulli V, Rhodes C, Diaferia G, Montgomery AM. Impact of defined matrix interactions on insulin production by cultured human beta-cells: effect on insulin content, secretion, and gene transcription. Diabetes 2006;55:2723–2729
43. Epifano C, Perez-Moreno M. Crossroads of integrins and cadherins in epithelia and stroma remodeling. Cell Adhes Migr 2012;6:261–273
44. Weber GF, Bjerke MA, DeSimone DW. Integrins and cadherins join forces to form adhesive networks. J Cell Sci 2011;124:1183–1193
45. Amin E, Dubey BN, Zhang SC, et al. Rho-kinase: regulation, (dys)function, and inhibition. Biol Chem 2013;394:1399–1410
46. Hammar E, Tomas A, Bosco D, Halban PA. Role of the Rho-ROCK (Rho-associated kinase) signaling pathway in the regulation of pancreatic beta-cell function. Endocrinology 2009;150:2072–2079
47. Parnaud G, Hammar E, Ribaux P, Donath MY, Berney T, Halban PA. Signaling pathways implicated in the stimulation of beta-cell proliferation by extracellular matrix. Mol Endocrinol 2009;23:1264–1271